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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/601,096	06/20/2003	Shin-Fuw Lin	3551.1000-000	9759

21005 7590 12/16/2004

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EXAMINER	
VENCI, DAVID J	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 12/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/601,096	LIN ET AL.	
	Examiner	Art Unit	
	David J Venci	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02/17/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *2/17/04* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Information Disclosure Statement

The entire list of pending U.S. patent applications accompanying Applicants' PTO-1449 submission of November 13, 2003 have been considered.

Drawings

The drawings are objected to because the description of Fig. 6 in the specification (pp. 31-32) does not appear to correspond to the information presented in Fig. 6. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. The replacement sheet(s) should be labeled "Replacement Sheet" in the page header (as per 37 CFR 1.84(c)) so as not to obstruct any portion of the drawing figures. If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1, 3, 6, 10, 22, 25, 28 and 34-35, the recitations of "optionally" or "optional" are indefinite. It is not clear whether verbiage subsequent to "optionally" or "optional" contain required claim limitations.

In claims 1, 3 and 6, the recitation of "wherein steps (a) through (d) are performed for a number of times" is indefinite. The purpose or necessity of repeatedly performing "acquiring" step (a) is not clear when the sample has already been acquired once. The purpose or necessity of repeatedly performing "separating" step (b) is not clear when the sample has already been separated once. The purpose or necessity of repeatedly performing "denaturing" step (c) is not clear when the sample has already been denatured once. Step (d) is further indefinite because it is not clear whether/how "pre-focusing" step is performed concurrently to steps (a) through (c). In claim 25, the recitation of "wherein steps (a) through (g) are performed for a number of times" is indefinite for similar reasons.

In claims 1, 3, 6 and 25, the recitation of "the level of detection" lacks antecedent basis. In claims 1 and 3, the recitation of "the level of detection" is further indefinite because a person of skill in the art cannot ascertain the standard or degree of "the level of detection" when no detection means is claimed.

In claims 3, 6, step (e), the recitation of "cleared sample" is indefinite because it is not clear whether said "cleared sample" corresponds to the "cleared sample" upon completion of step (c) or the pre-focused molecular species created in step (d). It is not clear how a "cleared sample" is electrophoretically separated after it has been pre-focused or whether a "cleared sample" ceases to exist after step (d). In claims 25 and 35, step (h), the recitation of "cleared sample" is indefinite for similar reasons.

In claims 8-9, 13-14, 19-20, 27-29, 33 and 35-37, the recitation of "about" is a relative term that renders the claim indefinite. The term "about" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

In claims 18, 25 and 32, the recitations of "acidity" or "acidities" are indefinite because it is not clear what compound(s) comprise a determination or adjustment of "acidity".

In claim 21, the recitation of "the low-electrolyte buffer" lacks antecedent basis.

In claim 34, the recitations of "the boundary" and "the low-electrolyte plug" lack antecedent bases.

In claim 35, step (d)(i) appears to have a formatting error, and step (f)(iii) appears to have a grammatical error (line 14). In addition, in step (f)(iii), the recitation of "a low-electrolyte aqueous solution plug having the acidity" lacks antecedent basis.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-16, 23-30 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schneider et al. (US 6,537,432) in view of Palmarsdottir et al., 688 J. CHROMATOGR. B. 127 (1997).

Schneider et al. teach a method of preparing a crude sample (see col. 5, lines 20-21, "proteins in complex mixtures from native cells and tissue samples") for detecting at least one molecular species of interest (see col. 3, line 24, "detection methods") comprising the steps of: acquiring a crude sample containing at least one molecular species of interest, one or more rough components that are larger than the molecular species of interest (see col. 23, lines 11-12, "cellular debris"), and one or more fine components that are smaller than the molecular species of interest (see col. 23, lines 17-18, "ionic strength"), separating at

least a portion of the rough component (see col. 23, line 16, "centrifugation"), separating at least a portion of the fine components (see col. 23, line 18, "dialysis"), denaturing the molecular species of interest contained in a cleared sample (see col. 30, lines 47-50, "homogenate is filtered or centrifuged to remove cellular debris... the proteins therein denatured"), and pre-focusing the molecular species of interest (see col. 17, lines 57-63).

Schneider et al. do not teach a method "wherein steps (a) through (d) are performed for a number of times sufficient to bring the concentration of at least one molecular species of interest in the sample up to the level of detection."

However, Palmarsdottir et al. teach a stacking method for increasing the concentration of a molecular species of interest (see Abstract). Furthermore, Palmarsdottir et al. teach a stacking method that is performed a number of times (see Title, "double stacking") and a double stacking method that is performed a number of times (see p. 133, col. 1, line 8, "double injections").

Therefore, it would have been obvious for a person of ordinary skill in the art to modify the pre-focusing method of Schneider et al. with the double-injection, double-stacking method of Palmarsdottir et al. because Palmarsdottir et al. observed detection limits in the low nM range without significant loss of separation performance (see Abstract).

With respect to claims 2, 4, 7, 16, 25 Palmarsdottir et al. teach a method further comprising removing insoluble contaminants by centrifugation (see p. 129, col. 1, "centrifuged for 10 min").

With respect to claim 3, Palmarsdottir et al. teach a method of preparing a crude sample for detecting at least one molecular species of interest comprising the steps of: electrophoretically separating the molecular species of interest in the cleared sample (see Title, "capillary electrophoresis") and detecting the separated molecular species of interest (see Fig. 3).

With respect to claims 5 and 26, Palmarsdottir et al. teach a method wherein the molecular species of interest is a small molecule (see Title, "bambuterol").

With respect to claim 6, Palmarsdottir et al. teach a method of preparing a crude sample for detecting at least one molecular species of interest comprising the steps of: introducing the cleared sample into a separation device comprising a capillary (see Title, "capillary") at least partially filled with a high-electrolyte buffer (see p. 130, col. 1, "5 mM phosphate buffer pH 7.5"), said capillary having an inlet end (see p. 130, col. 1, "capillary inlet") and an outlet end (see p. 130, col. 1, "outlet of the capillary"), a means for applying voltage (see p. 129, col. 2, "high-voltage power supply"), and a means for applying pressure differential (see p. 130, col. 1, "a facility which allows for applying a back-pressure").

With respect to claims 8-9 and 27, Schneider et al. teach a method wherein the sample acidity is adjusted to between about 5 and about 7 pH units or to about 5.5 to about 6.5 pH units (see col. 18, lines 1-13).

With respect to claims 10-15 and 28-30, Schneider et al. teach a method wherein the molecular species of interest is denatured (see col. 30, lines 47-50, "homogenate is filtered or centrifuged to remove cellular debris... the proteins therein denatured") with urea (see col. 11, line 58), sodium dodecyl sulfate detergent (see col. 17, lines 9-10) and heating (see col. 12, lines 20-22) from about 1 minutes to about 10 minutes at a temperature from about 60°C to about 100°C (see col. 12, lines 20-23). With respect to claims 13-14 and 28-29, it would have been obvious to a person of ordinary skill in the art to have modified the temperature from 60°C to 100°C, including 90°C, and duration of heating from 1 minute to 10 minutes, including 2 minutes, in order to denature a molecular species, since it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. See *In re Aller,* 105 USPQ 233 (CCPA 1955).

With respect to claims 23 and 24, Palmarsdottir et al. teach a method wherein CZE is performed (see Abstract) by applying a voltage (see p. 129, col. 2, "high-voltage power supply") between the inlet end (see p. 130, col. 1, "capillary inlet") and the outlet end (see p. 130, col. 1, "outlet of the capillary") of the capillary.

With respect to claim 25, Palmarsdottir et al. teach a method of detecting at least one molecular species of interest comprising the step of adjusting the acidity of the cleared sample (see p. 129, col. 2, "bambuterol molecules diffuse through the membrane liquid into the stagnant acidic acceptor phase").

With respect to claim 34, Palmarsdottir et al. teach a method comprising a capillary having an inlet end (see p. 130, col. 1, "capillary inlet") and an outlet end (see p. 130, col. 1, "outlet of the capillary"), a means for applying voltage (see p. 129, col. 2, "high-voltage power supply"), and a means for applying a pressure differential (see p. 130, col. 1, "a facility which allows for applying a back-pressure"). Schneider et al. teach the step of desalting (see col. 23, lines 27-29). The result of "electrophoretic migration of at least one molecular species in the cleared sample up to the boundary between the low-electrolyte plug and the high-electrolyte buffer, thereby pre-focusing" is necessarily present in the field amplified sample injection method of Chien & Burgi, and would be so recognized by persons of ordinary skill in the art.

Claims 17-22 and 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schneider et al. (US 6,537,432), in view of Palmarsdottir et al., 688 J. CHROMATOGR. B. 127 (1997) as applied to claims 1-16, 23-30, and further in view of Chien & Burgi, 559 J. CHROMATOGR. 141 (1991).

Schneider et al. and Palmarsdottir et al. teach a method of detecting a molecular species of interest as substantially described supra. The aforementioned references do not teach the step of "introducing a low-electrolyte plug into said separation device."

However, Chien & Burgi teach the step of introducing a low-electrolyte plug (see Abstract, "short plug of water") in order to improve the electric field amplification between the high-conductivity buffer and the low-conductivity sample solution (see Abstract).

Therefore, it would have been obvious for a person of ordinary skill in the art to modify the method of detecting a molecular species of interest, as taught by Schneider et al. and Palmarsdottir et al., with the use of a low-electrolyte plug because Chien & Burgi observed a 100-fold enhancement in the amount of ions injected (see Abstract) with no loss in peak resolution (see p. 142).

With respect to claims 18 and 32, Chien & Burgi teach a method of detecting a molecular species of interest wherein the low-electrolyte plug (see Abstract, "short plug of water", pH is undefined) has an acidity that is substantially different from that of the high-electrolyte buffer (see p. 146, "a buffer of 2-N-(morpholino)ethanesulfonic acid (MES) and histidine (HIS) at pH 6.2").

With respect to claims 19-20 and 33, it would have been obvious to a person of ordinary skill in the art to modify the pH of the high-electrolyte buffer to a pH of 7 to 9, including 7.5 to 8.5, in order to improve injection amount or peak resolution, since it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. See *In re Aller,* 105 USPQ 233 (CCPA 1955).

With respect to claim 22, Palmarsdottir et al. teach a method comprising a capillary having an inlet end (see p. 130, col. 1, "capillary inlet") and an outlet end (see p. 130, col. 1, "outlet of the capillary"), a means for applying voltage (see p. 129, col. 2, "high-voltage power supply"), and a means for applying a negative pressure differential (see p. 130, col. 1, "a facility which allows for applying a back-pressure"). Schneider et al. teach the step of desalting (see col. 23, lines 27-29). The result of "electrophoretic migration of at least one molecular species in the cleared sample up to the boundary between the low-electrolyte plug

and the high-electrolyte buffer, thereby pre-focusing" is necessarily present in the field amplified sample injection method of Chien & Burgi, and would be so recognized by persons of ordinary skill in the art.

Claims 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schneider et al. (US 6,537,432) in view of Chien & Burgi, 559 J. CHROMATOGR. 141 (1991).

Schneider et al. teach a method of detecting at least one protein species of interest (see col. 3, lines 2-4) in a crude sample (see col. 5, lines 20-21, "proteins in complex mixtures from native cells and tissue samples") comprising the steps of: acquiring a crude sample containing at least one molecular species of interest, one or more rough components that are larger than the molecular species of interest (see col. 23, lines 11-12, "cellular debris"), and one or more fine components that are smaller than the molecular species of interest (see col. 23, lines 17-18, "ionic strength"), separating at least a portion of the rough component (see col. 23, line 16, "centrifugation"), separating at least a portion of the fine components (see col. 23, line 18, "dialysis"), adjusting the sample acidity to between about 5 and about 7 pH units (see col. 18, lines 1-13), denaturing that at least one protein (see col. 30, lines 47-50, "homogenate is filtered or centrifuged to remove cellular debris... the proteins therein denatured") with detergent (see col. 17, lines 9-10) and heating (see col. 12, lines 20-22), removing insoluble contaminants (see p. 129, col. 1, "centrifuged for 10 min"), introducing the sample into a separation device comprising a capillary (see col. 3, line 4, "capillary electrophoresis methods") at least partially filled with high-electrolyte buffer having a pH between 7.0 and 9.0 (see col. 13, lines 46-49), a means for applying pressure differential (see col. 12, line 39, "Hydrodynamic/Pressure Elution"), pre-focusing (see col. 17, lines 57-63), desalting (see col. 23, lines 27-29), electrophoretically separating the protein species (see col. 3, line 4, "capillary electrophoresis methods"), and detecting the separated protein species (see col. 3, line 14, "detection methods"). The step of applying voltage between the inlet end and the outlet end of the capillary is necessarily present in the method of Schneider et al. and would be so recognized by persons of ordinary skill in the art.

Schneider et al. do not teach the step of introducing "a low-electrolyte aqueous solution plug having the acidity of about 7.0 pH units" into said separation device.

However, Chien & Burgi teach the step of introducing a low-electrolyte plug (see Abstract, "short plug of water") in order to improve the electric field amplification between the high-conductivity buffer and the low-conductivity sample solution (see Abstract). The low-electrolyte water plug of Chien & Burgi has an acidity of *about* 7.0 pH units.

The result of "electrophoretic migration of at least one molecular species in the cleared sample up to the boundary between the low-electrolyte plug and the high-electrolyte buffer, thereby pre-focusing" is necessarily present in the field amplified sample injection method of Chien & Burgi, and would be so recognized by persons of ordinary skill in the art.

Therefore, it would have been obvious for a person of ordinary skill in the art to modify the method of detecting a molecular species of interest, as taught by Schneider et al., with the use of a low-electrolyte plug because Chien & Burgi observed a 100-fold enhancement in the amount of ions injected (see Abstract) with no loss in peak resolution (see p. 142).

With respect to claim 36, Schneider et al. teach a method comprising sodium dodecyl sulfate detergent (see col. 17, lines 9-10) and heating (see col. 12, lines 20-22) for about 2 minutes at about 90°C (see col. 12, lines 20-23).

With respect to claim 37, Chien & Burgi teach a method wherein the high-electrolyte buffer is *about* 7.0 to about 9.0 pH units (see p. 146, "a buffer of 2-N-(morpholino)ethanesulfonic acid (MES) and histidine (HIS) at pH 6.2").

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J Venci whose telephone number is 571-272-2879. The examiner can normally be reached on 08:00 - 16:30 (EST). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David J Venci
Examiner
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